

Applicants : Michael Wayne Graham and Robert Norman Rice
Serial No. : 10/646,070
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REMARKS

Claims 48, 107, 110, 111, 114 to 136, 138, and 146 to 149 were pending in the subject application, and claims 139, 140, 145, and 150 to 152 had been withdrawn. Applicants have amended claims 48, 110, 114 to 133, 139, 140, 146, 147, and 150 to 152 herein, and have canceled claims 107 and 111 without prejudice or disclaimer to applicants' rights to pursue the subject matter of these claims in this or another application.

Support for Amendments to Claims 48, 110, 114 to 133, 139, 140, 146, 147, and 150 to 152

Applicants have amended claims 48, 120, 122, 124, 126, 128, 130, 133 to 136, 138, 139, 146, and 148 to 152 herein to recite a "double-stranded" synthetic gene, and claims 110, 114 to 119, 121, 123, 125, 127, 129, 131, 132, and 140, 145, and 147 herein to recite a "double-stranded" synthetic genetic construct. Applicants note that the subject application is a continuation of the § 371 national stage of PCT International Application No. PCT/AU99/00195, filed March 19, 1999, which claims priority, *inter alia*, of Australian Provisional Patent Application No. PP2499, filed March 20, 1998 (the "2499 Application"). Support may be found on page 17, lines 17 to 20, of the 2499 Application, when taken together with the definition of "palindrome." See **Exhibit A.**

Additionally, the specification of the subject application as originally filed and the 2499 Application is replete with examples of a "double-stranded synthetic gene" and a "double-stranded synthetic genetic construct". For example, see page 31, lines 3 to 6, of the 2499 Application (referring to blunt-ended

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fragments); and page 46, lines 13 to 14 (referring to production of plasmid pCR2.BEV.2).

In view of the forgoing, applicants respectfully maintain that the above-cited sections of the specification of the subject application as originally filed, and the 2499 Application fully support, *inter alia*, the language "double-stranded".

Additionally, applicants have amended claims 110 and 119, *inter alia*, to correct the antecedent bases of language in the claims, and have amended claim 119, *inter alia*, to correct a typographical error.

Applicants have canceled claims 107 and 111 without prejudice or disclaimer to applicants' rights to pursue the subject matter of these claims in this or another application. After entry of this Amendment, claims 48, 107, 110, 111, 114 to 136, 138, and 146 to 149, as amended herein, will be pending in the subject application and claims 139, 140, 145, and 150 to 152 will have been withdrawn.

Information Disclosure Statement

The Examiner indicated that the information disclosure statement (IDS) submitted on October 29, 2007 is in compliance with the provisions of 37 C.F.R. § 1.97 and is being considered by the Examiner.

The Examiner, however, indicated that some of the articles or documents listed on the information disclosure statement filed October 29, 2007 fail to comply with the provisions of 37 C.F.R.

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§§ 1.97 and 1.98, and M.P.E.P. § 609 because several citations are missing the title and several documents are missing a publication date.

Applicants' Response

In response, applicants refer the Examiner to the Supplemental Information Disclosure Statement herein, and respectfully request consideration of all items disclosed.

Claim Objections

The Examiner objected to claims 107 and 111 under 37 C.F.R. § 1.75(c), as allegedly of improper dependent form for failing to further limit the subject matter of a previous claim.

Applicant's Response

In response, without conceding the correctness of the Examiner's position and in order to expedite prosecution, applicants have canceled claims 107 and 111 to applicants' rights to pursue the subject matter of these claims in this or another application.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph - Definiteness

The Examiner rejected claims 48, 107, 110, 111, 114 to 136, 138, and 146 to 149 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention, and as allegedly incomplete for omitting essential

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structural cooperative relationships of elements, such omission amounting to a gap between the necessary structural connections, referencing M.P.E.P. § 2172.01.

The Examiner asserted that the omitted structural cooperative relationships are: how a gene comprising two identical sequences to a target gene in a vertebrate animal cell can also be arranged as an interrupted palindrome sequence. The Examiner asserted that an interrupted palindrome sequence is a sequence and its complement, not two identical sequences, wherein one sequence is in the direct orientation and the other sequence is inverted. The Examiner asserted that the instant specification only recites the term and does not specifically define the term, referencing page 29. The Examiner asserted that the skilled artisan would understand the term as described above, referencing Abdurashitov, M.A., et al. (1997) "BstAPI, an ApaBI isoschizomer, cleaves DNA at 5'-GCANNNN↓NTGC-3'," Nucleic Acids Res. 25(12):2301, abstract only ("Abdurashitov et al. Abstract"), and referencing M.P.E.P. § 2173.02, which recites that:

Definiteness of claim language must be analyzed, not in a vacuum, but in light of:

- (A) The content of the particular application disclosure;
- (B) The teachings of the prior art; and
- (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

The Examiner indicated that claim 119 recites the limitation "wherein the viral vector is a retrovirus or a lentivirus" in line 2. The Examiner asserted that there is insufficient antecedent basis for this limitation in the claim. The Examiner

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indicated that the claim depends from claim 116 which does not recite the limitation, however, claim 118 does recite the limitation.

Applicants' Response

Initially, in response to the Examiners' objection to claim 119, applicants thank the Examiner for the careful review and have amended claim 119 to depend from claim 118.

In response to the Examiner's rejection of claims 48, 107, 110, 111, 114 to 136, 138, and 146 to 149, applicants respectfully traverse.

The claims are clear and definite once the claims are understood to require double-stranded genes and constructs. Indeed, the very dilemma the Examiner exemplifies - "how a gene comprising two identical sequences . . . can also be arranged as an interrupted palindrome" - is not a dilemma but rather a requirement to interpret the claim to require double-stranded genes and constructs.

To make explicit that which the claims currently require, applicants have amended claims 48, 120, 122, 124, 126, 128, 130, 133 to 136, 138, 139, 146, and 148 to 152 to recite a "double-stranded synthetic gene", and claims 110, 114 to 119, 121, 123, 125, 127, 129, 131, 132, 140, 145 and 147 to recite a "double-stranded synthetic genetic construct".

With respect to the term "palindrome" applicants respectfully submit that the term is used in this application consistently

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with its art recognized meaning. See, e.g., page 29, lines 25 to 28, of the specification of the subject application as originally filed, and page 17, lines 17 to 19, of the 2499 Application and **Exhibit A**, hereto. Based on the January 24, 2008 Office Action the Examiner appears to understand the term consistent with its art recognized meaning.

To facilitate understanding, applicants also attach hereto as **Exhibit C** diagram "C" of a "double-stranded synthetic gene" or a "double-stranded synthetic genetic construct" with an "interrupted palindrome sequence".

Applicants respectfully submit that many of the rejections in the January 24, 2008 Office Action are obviated once the "synthetic gene" or "synthetic genetic construct" of the claimed invention is properly understood to be a "double-stranded genetic construct" or a "double-stranded synthetic genetic construct". A "genetic construct" or a "synthetic genetic construct" can have a "copy" of a structural gene region in the sense and a "copy" in the antisense orientation which copies are also arranged as an interrupted palindrome when the "genetic construct" or a "synthetic genetic construct" is double-stranded. Applicants further submit that the disclosure of Abdurashitov et al. Abstract, which the Examiner referenced in the January 24, 2008 Office Action, can be understood consistently with applicants' usage of the term palindrome (although ultimately the usage in the unrelated Abdurashitov et al. Abstract is not relevant to the subject application).

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 48, 107, 110,

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111, 114 to 136, 138, and 146 to 149 as allegedly indefinite and
allegedly incomplete.

Claim Rejections Under 35 U.S.C. § 102(e) - Fire et al.

The Examiner maintained the rejection of claims 48, 107, 108, 110, 111, 114 to 118, 120, 121, 124 to 136, and 146 to 149 under 35 U.S.C. § 102(e) as allegedly anticipated by Fire et al. (U.S. Patent No. 6,506,559, disclosed on a Form PTO-1449 (Substitute)) ("Fire et al. Patent").

Applicants' Response

In response, applicants respectfully traverse.

1. Fire et al. Patent is not prior art to the claimed invention

As an initial matter, Fire et al. Patent is not prior art to the subject application. To summarize, the claims of the subject application are entitled to the priority of the March 20, 1998 filing date of the 2499 Application. Fire et al. Patent issued from an application submitted to the United States Patent and Trademark Office on December 23, 1998, *i.e.* after the priority date of the subject application.

Fire et al. Patent claims the benefit of U.S. Provisional Application No. 60/068,562, filed December 23, 1997 ("Fire et al. Provisional.") However, Fire et al. Provisional discloses less than Fire et al. Patent. Applicants attach hereto as **Exhibit D** a copy of Fire et al. Patent marked-up to show differences from Fire et al. Provisional. Accordingly, any rejection under 35

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U.S.C. §§ 102 and 103 can at most be based on the disclosure of Fire et al. Provisional carried forward, not on the disclosure of Fire et al. Patent.

The January 24, 2008 Office Action cites numerous portions of Fire et al. Patent which do not appear in Fire et al. Provisional. The rejections which rely on disclosures not in Fire et al. Provisional are clearly improper.

Accordingly, this discussion proceeds to analyze the disclosure in the Fire et al. Provisional.

2. Fire et al. Provisional does not recite all of the elements of the claimed invention arranged as in the claim

It is well settled that "[a]nticipation requires the presence in a single prior art disclosure of all elements of a claimed invention *arranged as in the claim*." *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983) (emphasis added) (citing *Soundsciber Corp. v. U.S.*, 360 F.2d 954, 960 (Ct. Cl. 1966) (copy attached hereto as Exhibit E). A copy of *Connell* is attached hereto as Exhibit F. Fire et al. Provisional fails to disclose all elements of the claimed invention in this required arrangement.

Specifically, the Fire et al. Provisional does not disclose a "double-stranded" molecule with an "interrupted palindrome".

Applicants understand that the most relevant portion of Fire et al. Provisional appears on page 6, line 19: "[t]he double-stranded structure may be formed by a single self-complementary RNA strand or multiple complementary RNA strands". This

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disclosure does not anticipate the claimed invention at least because it is not a disclosure of a "double-stranded synthetic gene" or "double-stranded synthetic genetic construct", as recited by applicants' claims.

Page 7, lines 13 to 15, of Fire et al. Provisional disclose that "[f]or transcription from a transgene *in vivo* or an expression vector, a regulatory region (e.g., promoter, enhancer, silencer) is used to transcribe the RNA strand(s)" (*italics in original*). Page 11, lines 19 and 20, of Fire et al. Provisional disclose that "[t]he use and construction of an expression vector are known in the art" (citations omitted). However, these disclosures do not specify whether the "expression vector" of Fire et al. Provisional is i) double-stranded; or ii) has an "interrupted palindrome sequence".

i. Fire et al. Provisional does not disclose double-stranded constructs, expressly or inherently

"A single self-complementary RNA strand" can be expressed by a single-stranded vector *in vivo*. For example, viroids are pathogens which are circular single-stranded RNA molecules (see, e.g., Gross, H.J., et al. (1982) "Nucleotide sequence and secondary structure of citrus exocortis and chrysanthemum stunt viroid," Eur. J. Biochem. 121(2):249-57, a copy of which is attached hereto as **Exhibit G**). Viroids can be used to produce *in vivo* a "single self-complementary RNA strand." Therefore, the disclosure of a transgene or expression vector (at page 7, lines 13 to 15, and at page 11, lines 19 and 20), even if properly connected to the disclosure of a single self-complementary RNA strand (page 6, line 19), is not a disclosure of a double-stranded construct. Nothing in the Fire et al.

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Provisional further defines the disclosure of transgenes or expression vectors. As such, this disclosure can just as reasonably be a disclosure of a single-stranded vector, i.e. it is a generic disclosure.

It is well settled that a generic disclosure does not anticipate a species within the genus. See, e.g., *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1377 (Fed. Cir. 2006) (an enantiomer of a compound is novel over the disclosure of the racemate) (copy attached hereto as Exhibit H).

Accordingly, the Fire et al. Provisional does not anticipate the "double-stranded" molecules claimed in the subject application.

ii. Fire et al. Provisional does not disclose an "interrupted palindrome"

The Fire et al. Provisional does not specify whether the "transgene" or "expression vector" disclosed on page 7, lines 13 to 15, or page 11, lines 19 and 20 of Fire et al. Provisional could have an "interrupted palindrome." The "interrupted palindrome" is an element which is distinct from the "structural gene region" element in applicants' claims. Under the broadest interpretation, the Fire et al. Provisional discloses that the "transgene" or "expression vector" can be used to make the "single self-complementary RNA strand." However, the Fire et al. Provisional does not disclose that the "single self-complementary RNA strand" has a central portion that is not "self-complementary."¹ Indeed, an interpretation of "self-complementary" in Fire et al. Provisional that includes a central

¹ The "loop" of a self-hybridized RNA will form regardless of whether the nucleotides of the "loop" are self-complementary.

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non-self-complementary segment of nucleotides is arbitrary and hints of hindsight bias. It is therefore applicants' position that the Fire et al. Provisional does not anticipate the double-stranded molecules having an "interrupted palindrome sequence" as claimed in the subject application.

Applicants note the Examiner's continued reliance on the "loop" of a hairpin molecule to assert that the gene construct would have an interrupted palindrome. Importantly, however, a "loop" in a hairpin will form regardless of whether the palindromic sequence encoding the hairpin contains an interruption or not.

Thus, even if it were reasonable to broadly interpret Fire et al. Provisional to allow for the possibility of a *non-self-complementary* segment of nucleotides in its "single self-complementary RNA strand" (and a consequent segment in the "expression vector" of Fire et al. Provisional), such an interpretation only leads to the conclusion that Fire et al. Provisional is a disclosure generic to a genetic construct with an "interrupted palindrome."

Discussion

For purposes of clarity in this discussion, applicants provide the following discussion in order to assist in an understanding of the meaning conveyed to persons skilled in the art of certain terms. To assist in this, applicants attach hereto as Exhibit C, diagram "C" of a "double-stranded synthetic gene" or a "double-stranded synthetic genetic construct" with an "interrupted palindrome sequence".

The term "self-complementary" is an adjective and, in relevant

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context, provides information about the single RNA strand. "Self-complementary" informs the reader that the single RNA strand has segments of nucleotides that have the ability to hybridize, under appropriate conditions. It does not inform the reader of, *inter alia*, how many such segments there are; how many nucleotides are in each segment; how many nucleotides in the segment have the ability to hybridize; and whether any different segments are present. The term "self-complementary" also does not indicate whether the single RNA strand is self-hybridized.

When a self-complementary RNA strand is self-hybridized it may form what is referred in the art as a "hairpin" structure owing to its resemblance when represented on paper to a hairpin. When it is self-hybridized, such a self-hybridized RNA strand is commonly referred to as a "hairpin RNA" or more generally, a "hairpin oligonucleotide."

A hairpin oligonucleotide usually has a non-hybridized portion termed a "loop." Importantly, the "loop" results *regardless* of whether the nucleotides constituting the "loop" are self-complementary or not².

Thus, the "loop" the Examiner continues to rely on will form regardless of whether the construct encoding the hairpin contains an interrupted palindrome. For example, a construct without an interrupted palindrome will encode a single-stranded self-complementary RNA without a non-self-complementary segment between the complementary segments; such a self-complementary

² Because the "loop" is a single stranded segment, the "interrupted palindrome" element of the pending claims cannot be construed to read on a hairpin with a "loop." The interrupted portion of the "interrupted palindrome" is double-stranded, while the "loop" of a hairpin oligonucleotide is never double-stranded.

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single-stranded RNA would nonetheless form a "loop" when in a hairpin conformation. The Fire et al. Provisional clearly encompassed such constructs in its disclosure of "transgene" and "expression vector."

Accordingly, Fire et al. Provisional does not disclose double-stranded constructs comprising interrupted palindrome sequences, but is instead at most a generic disclosure that includes double-stranded constructs without interrupted palindrome sequences. Such a generic disclosure does not anticipate applicants' pending claims. See, e.g., *Sanofi-Synthelabo*, 470 F.3d at 1377.

Accordingly, the anticipation rejection on pages 5 to 9 of the January 24, 2008 Office Action is improper and should be withdrawn.

Claim Rejections Under 35 U.S.C. § 103(a) - Fire et al. Patent in view of Dietz

The Examiner rejected claims 48, 110, 116, 117, 119, 122, and 123 under 35 U.S.C. § 103(a) as allegedly unpatentable over Fire et al. Patent taken with Dietz (U.S. Patent No. 5,814,500).

Applicants' response

In response, applicants respectfully traverse.

Applicants respectfully maintain that Dietz does not remedy any of the defects of Fire et al. Provisional discussed in applicants' response to the 35 U.S.C. § 102(e) rejection herein.

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Nothing in Dietz or Fire et al. Provisional teaches one of skill in the art to select applicants' claimed combination of elements. Neither Dietz or Fire et al. Provisional or the general knowledge of the field at the time (which was nascent) provided "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does." *KSR*, 127 S.Ct. at 1741.

Accordingly, applicants respectfully submit that a *prima facie* case of obviousness cannot be made based on Dietz and Fire et al. Provisional and request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections Under 35 U.S.C. § 103(a) - Fire et al. Patent in view of Ladner et al.

The Examiner rejected claims 133, 136, and 138 under 35 U.S.C. § 103(a) as allegedly unpatentable over Fire et al. Patent and taken with Ladner et al. (U.S. Patent No. 5,198,346). The Examiner asserted that Fire et al. Patent teaches a vector comprising a construct comprising a promoter operably linked to a nucleotide sequence comprising a sense strand and an antisense strand of the target gene (columns 4 and 9). The Examiner asserted that that a viral vector can be used as the vector (column 9).

The Examiner acknowledged that however, Fire et al. Patent does not specifically teach separating a construct comprising the structural gene sequences with a stuffer sequence.

The Examiner asserted that at the time the invention was made,

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Ladner et al. taught using a stuffer fragment having above about 10 nucleotides to introduce a stop codon or a unique restriction site (Table 704).

The Examiner asserted that it would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire et al. Patent taken with Ladner et al., namely to produce a construct comprising a structural gene with a stuffer sequence having above about 10 nucleotides. The Examiner asserted that one of ordinary skill in the art would have been motivated to combine the teaching "to introduce a termination site after the sense strand or a unique restriction sequence for cloning purposes."

The Examiner asserted that in view of Fire et al. Patent and Ladner, one of ordinary skill in the art would have had a reasonable expectation of success for producing the product. The Examiner asserted that therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicants' Response

In response, applicants respectfully traverse. Applicants maintain that the Examiner's combination of Fire et al. Provisional and Ladner et al. purports to solve a problem that was simply not identified in the Fire et al. Provisional, in Ladner et al., or in the nascent field.

Applicants note that the claimed invention does not recite a "stuffer fragment". Even if the Examiner equates the "stuffer

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sequence" of Ladner et al. with the "interruption" of the "interrupted palindrome sequence" of the claimed invention, applicants note that the viral vectors of Fire et al. Provisional do not require a stuffer fragment.

There is no reason to combine the elements of Fire et al. Provisional and Ladner et al.

The Examiner asserted that the reason to combine the elements of Fire et al. Provisional and Ladner et al. was "to introduce a termination site after the sense strand or a unique restriction sequence for cloning purposes." Applicants maintain that the viral vectors of Fire et al. Provisional are for the production of RNA for RNA interference, rather than "cloning purposes". There is no rationale for introducing a termination site or a unique restriction site between relevant portions of the Fire et al. transgene or expression vector. There is simply no articulated problem with the Fire et al. Provisional which Ladner et al. purports to solve.

An obviousness rejection cannot be proper unless it identifies "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed invention does." *KSR*, 127 S.Ct. at 1741.

Applicants therefore respectfully maintain that the combination of the "stuffer sequence" disclosed by Ladner et al. for the purpose of introducing stop codons, a frame shift, and a unique restriction site into an unspecified portion of the transgene of Fire et al. Provisional is arbitrary at best and hints of hindsight bias.

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Accordingly, applicants respectfully maintain the combination of the Fire et al. Provisional with Ladner et al. cannot support a *prima facie* case of obviousness of the claimed invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Double Patenting Rejections

The Examiner rejected claims 48, 107, 110, 111, 114 to 121, 124 to 136, 138, and 146 to 149 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 to 6, 11 to 15, and 19 to 21 of U.S. Patent No. 6,573,099. The Examiner asserted that although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims are directed to a construct capable of producing dsRNA.

The Examiner provisionally rejected claims 48, 107, 110, 111, 114 to 121, 124 to 136, 138, and 146 to 149 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 56, 59, 60, 62, 63, 65-67, 77 to 90, 95 to 101, and 107 of copending Application No. 09/646,807. The Examiner asserted that although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims read on an animal cell comprising a construct comprising two identical sequences to a target gene in an animal. The Examiner asserted that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The Examiner provisionally rejected claims 48, 107, 110, 111, 114

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to 121, 124 to 136, 138, and 146 to 149 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims from copending Application Nos. 10/346,853 and 11/364,183. The Examiner alleged that although the conflicting claims are not identical, they are not patentably distinct from each other because both set of claims read on an animal cell comprising a construct comprising two identical sequences to a target gene in an animal. The Examiner alleged that this is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicants' Response

In response, applicants thank the Examiner for the careful review. However, applicants respectfully defer discussion of the rejections until the obviousness-type double patenting rejections are the only rejection remaining in the present application. M.P.E.P. § 804(I)(B).

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SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

In accordance with their duty of disclosure under 37 C.F.R. § 1.56, applicants direct the Examiner's attention to the following references which are listed on the Form PTO-1449 (Substitute) attached hereto as **Exhibit I**.

Applicants note that the Examiner struck certain references from the initialed Form PTO-1449 (Substitute) included with the January 24, 2008 Office Action. Applicants have listed certain of these references on the attached Form PTO-1449 (Substitute). Applicants have also included the year of publication and titles of the references.

The Examiner is respectfully requested to make these references of record in the subject application by initialing and returning a copy of the enclosed substitute Form PTO-1449.

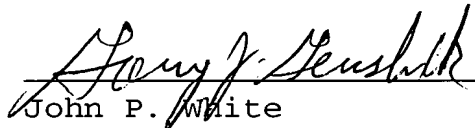
According to 37 C.F.R. § 1.97(c) an Information Disclosure Statement filed after the period specified in 37 C.F.R. § 1.97(b) shall be considered if accompanied by the fee set forth in the 37 C.F.R. § 1.17(p) or a statement under 37 C.F.R. § 1.97(e). The required fee set forth in 37 C.F.R. § 1.97(p) is one hundred and eighty dollars (\$180.00) and a check including this amount is enclosed.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

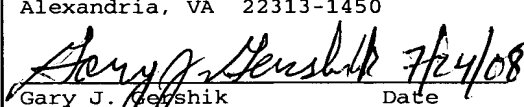

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No fee, other than the enclosed fees of \$1,050.00 for a three-month extension of time and \$180.00 for filing a Supplemental Information Statement, is deemed necessary in connection with the filing of this Amendment. However, if any fee is required authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,


John P. White

Registration No. 28,678
Gary J. Gershik
Registration No. 39,992
Attorneys for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400

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